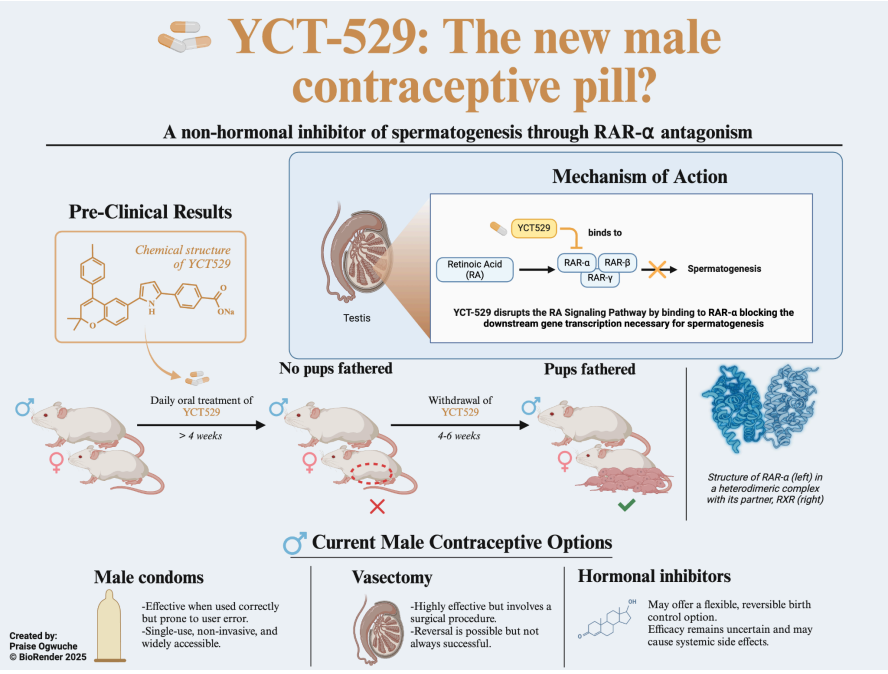
Executive Summary - YCT-529: A Potential Male Contraceptive Pill

Male contraception remains limited, with no widely available oral options. YCT-529, a non-hormonal RAR-α inhibitor, shows promise in disrupting spermatogenesis. My Capstone explores its potential through:

Part 1: Literature Review

My review evaluated YCT-529's potential as a non-hormonal male contraceptive by analyzing its molecular mechanism, efficacy, and reversibility. YCT-529 selectively binds RARα, outcompeting retinoic acid (RA) and stabilizing its helix 12 domain in its inactive conformation, thereby repressing RA-dependent transcription essential for spermatogenesis. In murine models, daily oral dosing induced complete infertility within four weeks by halting sperm production. Fertility fully recovered 4–6 weeks post-withdrawal, with no systemic toxicity or hormonal disruption. Unlike hormonal methods, YCT-529 offers receptor-specific targeting with minimal side effects, supporting its promise as a precise, reversible, and safe male contraceptive agent.



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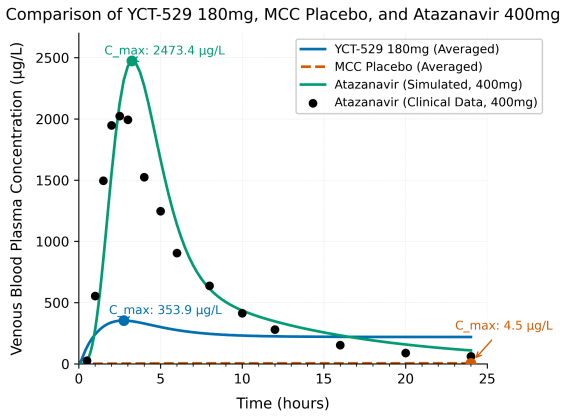
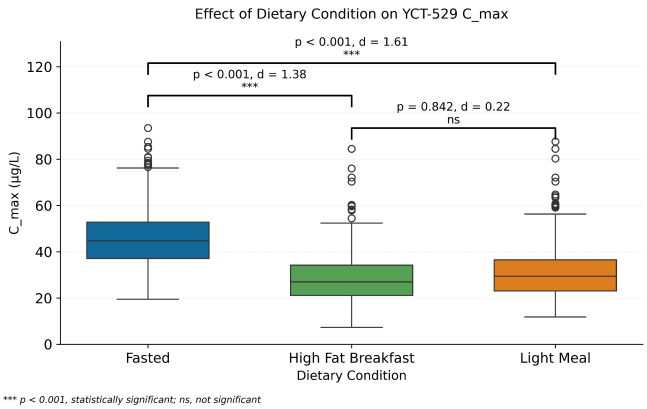
Part 2: Pharmacokinetic Modeling

Using PBPK modeling in PK-Sim and ADMETLab, I simulated YCT-529 pharmacokinetics in 16,000 virtual individuals. Systemic exposure increased with dose, reaching approximately 500 μg/L at 180 mg. Population differences emerged: East Asians exhibited the highest Cmax and slower clearance, suggesting lower dosing ranges (e.g., 45 mg) may suffice, while Black Americans—who had the lowest exposure—may require higher doses (e.g., 180 mg) at shorter intervals. These findings recommend race-informed dose ranges in early clinical trials. Model validation using Atazanavir also confirmed simulation reliability via alignment with clinical data.

Dietary state significantly altered systemic exposure: fasting raised mean Cmax to 45.85 μg/L, versus 30.58 μg/L (light meal) and 28.32 μg/L (high-fat), with large effect sizes (Cohen's d = 1.38–1.61) and $p < 0.001$. This supports fasting administration to maximize early exposure. However, plasma levels converged at approximately 40 μg/L beyond 10 hours, suggesting steady-state outcomes may be diet-independent. Clinically, these simulations recommend stratifying participants by dietary state and ethnicity in Phase I trials to optimize dose-response analysis and assess adherence feasibility.





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YCT-529 shows potential as a male contraceptive, but clinical trials are needed to confirm efficacy and assess dietary effects on systemic exposure and absorption. My work provides a foundation for future research.